Atty's Docket: 101137-31

## CONDITIONAL PETITION FOR EXTENSION OF TIME

If any extension of time for this response is required, Applicants request that this be considered a petition therefore. Please charge the required fee to Deposit Account No. 14-1263.

## ADDITIONAL FEES

Please charge any further insufficiency of fees, or credit any excess to Deposit Account No. 14-1263.

## REMARKS

Claims 1-11 are in the application. Examiner's objections and rejections will be addressed in the sequence presented in the office action.

Claim 1 was amended to include specify that there is a first and second separation step in the method. The term "first" was added prior to the first appearance of the phrase "separation step."

The objection to claim 11 has been rendered moot by amendment as suggested by the Examiner.

Indefiniteness

The term orphan receptor is known in the art as referring to a protein whose binding partners, i.e., ligands, have not yet been identified. This term is also defined in the first paragraph of page 1 in the specification.

Accordingly, withdrawal of this rejection is requested.

## THE CLAIMS ARE NOT ANTICIPATED BY NEDVED

### A. Nedved's "On-line" Method is not a Completely Automated On-line Series of Steps

It is respectfully suggested that Nedved cannot anticipate the claims because Nedved's disclosed series of steps, from forming affinity receptor-analyte complexes to directing the final purified analyte sample to the mass spectrometer, is not completely on-line as is Applicants'. Accordingly, the rejection should be withdrawn in view of all of the steps in Applicants' on-line method being completely automated; i.e., it is a "true" on-line method.

For example. Nedved clearly states that the third column step, i.e., C-8 Betasil, was performed by manually injecting the samples. See p. 4230, col. 1.

Further, Nedved does not disclose the means for an automated directing of the final analyte to the mass spectrometer. In fact, there is no disclosure of this step being automated at all.

Thus, Nedved's disclosed method, as applied by the Examiner in the rejection, does not actually encompass true on-line methodology over the entire series of steps analogous to those recited in the claims. See page 6, line 26, to page 7, line 8 for a general statement of the automation of the recited steps. Also, see page 13, lines 30 to page 14, line 5 for disclosure of automated delivery to the mass spectrometer.

It is respectfully suggested that Nedved cannot anticipate the claims as the disclosed method is not an automated on-line method for all the steps recited in the claims.

B. Nedved Does not Teach the Identical Arrangement of Steps

Claims 1-11 are deemed anticipated by the Nedved article.

In response, Applicants respectfully remind Examiner that anticipation requires that each and every element as set forth in the claim must be found, either expressly or inherently described, in a single prior art reference, and, further, that the absence in the prior art reference of even a single claim element precludes a finding of anticipation. *In re Robertson,* 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

Applicants further demonstrate that Nedved does not teach each of the claim limitations, and therefore cannot anticipate the claimed method.

The claimed method forms complexes between fractionated analyte effluent and putative receptors in solution. The resultant complexes are separated from the unbound analyte in a single step; i.e., the first separation using a restricted-access medium [RAM]. In contrast, Nedved forms the benzodiazepine-IgG complexes as an insoluble immobile phase by first loading an analyte mixture onto a protein G-agarose column that had already been saturated with anti-diazepine antibody. Therefore, Nedved does not teach the first two steps of the claimed method.

Further, after dissociating the putative receptor-analyte complexes, the claimed method employs one step to separate the putative affinity receptor from the dissociated analytes. In contrast, Nedved requires two of such steps. Nedved, p. 4229, bottom col. 2.

These differences in the methods are clearly sufficient to render the anticipation rejection improper. Withdrawal of the rejection is, therefore respectfully requested.

C. Nedved's Disclosure Cannot Enable the Claimed Method

It is well established that a proper reference under 35 USC §102 must be enabling in the sense of 35 USC §112, 1st paragraph. It is suggested that the Nedved reference is not enabling to that extent. Pertinent is the following quote from *In re Le Grice,* 133 USPQ 365, 374 (CCPA 1962):

> [T]he proper test of a description in a publication as a bar to a patent as the clause is used in section 102(b) requires a determination of whether one skilled in the art to which the invention pertains *could take the description of the invention in the printed publication and combine it with his own knowledge of the particular art and from this combination be put in possession of the invention* on which a patent is sought. [Emphasis added.]

For the reasons stated above, Nedved could not reasonably guide persons of ordinary skill in the art to arrive at the claimed method. There are far too many differences that would provide guidance to arrive at the claimed method.

In accordance with the foregoing amendments and remarks, it is suggested that the claims are in condition for allowance, and that allowance be granted.

Respectfully Submitted,

Norris, McLaughlin & Marcus
220 East 42 nd Street
New York, NY 10017
Telephone (212) 808-0700
Facsimile (212) 808-0844

Theodore Gottlieb, PhD
Reg. No. 42, 597

Certificate of Transmission

I hereby certify that this correspondence is being facsimile transmitted to the U.S. Patent and Trademark Office Fax No. (703 )872-9306

on 28 January 2004 .
(Date)

Theodore Gottlieb
Typed or printed name of person signing this certificate

Signature

IN THE CLAIMS

Please amend the claims as follows:

1. (Currently amended) On-line detection method comprising the on-line coupling of the effluent of a fractionation step to a mass spectrometer, which method comprises the addition of a controlled amount of an affinity molecule to said effluent, whereby the affinity molecules bind analytes in the effluent, followed by a first separation step using a restricted-access support, whereby the analyte-affinity molecule complex is permeated, followed by a suitable dissociation step to dissociate the analyte-affinity molecule complex, followed by a second separation step in which the dissociated analyte and affinity molecules are separated, followed by detection of the analyte using the mass spectrometer.

2. (Previously presented) On-line detection method according to claim 1, in which the second separation step is carried out using a restricted-access support, in which the affinity molecule is retained, followed by elution of the analyte from the restricted-access support using a suitable carrier stream, and directing the eluted stream to the mass spectrometer.

3. (Previously presented) On-line detection method according to claim 1, in which the second separation step is carried out using a hollow fiber support, whereby the analyte is permeated and the permeate is directed to the mass spectrometer.

4.(Previously presented) On-line detection method according to claim 1, in which the dissociation step is a low pH shock, contacting with a high ionic strength solution, contacting with an organic solvent and/or contacting with a chaotropic reagent.

5.(Previously presented) The method according to claim 1, in which the fractionation step is a liquid chromatography separation, a capillary electrophoresis step or a combinatorial chemistry system, which is optionally followed by a separation step which removes the high molecular weight background.

6. (Previously presented) The method according to claim 5, in which the liquid chromatography separation step is a HPLC, a reversed phase HPLC, a CE, a CEC, a IEF or a MEKC step.

7. (Previously presented) The method according claim 1, in which the mass spectrometer is of the type chosen from the group consisting of electrospray ionization type, atmospheric pressure ionization type, quadrupole type, magnetic sector type, time-off flight type, MS/MS, $MS^n$, FTMS type, ion trap type and combination thereof.

8. (Previously presented) The method according to claim 1, in which the mass spectrometer is set to detect ions of a selected single m/z trace, selected multiple m/z traces, in scanning mode or any sequential mode.

9. (Previously presented) The method according to claim 1, wherein the affinity molecule is an affinity protein.

10. (Previously presented) The method according to claim 1, wherein the affinity molecule is an orphan receptor.

11. (Currently amended) A compound detected by the method claim 1.

12. (Canceled)